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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/527,280

03/08/2005

Peter Bernstein

133087.12101(100829-1PUS)

3799

52286

7590

12/08/2008

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EXAMINER

O'DELL, DAVID K

ART UNIT

PAPER NUMBER

1625

MAIL DATE

DELIVERY MODE

12/08/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/527,280	Applicant(s) BERNSTEIN ET AL.	
	Examiner David K. O'Dell	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-6, 30 are pending in the current application.
2. This application is a 371 of PCT/SE03/01399 filed 09/08/2003, which claims priority to the following Swedish applications: 0202674-8 filed 09/09/2002 and 0301052-7 filed 04/08/2003.

Request for Continued Examination

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 26, 2008 has been entered.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

4. The rejection of claims 1-6 and newly added claim 30 under 35 U.S.C. 103(a) as being obvious over Harrison et. al. WO 94/110165, AND Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773 AND Hagiwara et. al. "Studies on Neurokinin Antagonists. 4. Synthesis and Structure-Activity Relationships of Novel Dipeptide Substance P Antagonists: N²-[(4R)-4-Hydroxy-1-([1-methyl-1H-indol-3-yl)carbonyl]-L-prolyl]-N-methyl-N-(phenylmethyl)-3-(2-naphthyl)-L-alaninamide and Its Related Compounds" *Journal of Medicinal Chemistry* **1994**, *37*, 2090-2099, is maintained and rephrased with further references added.

The applicants' representative has argued that the examiner is making the rejection over the compounds of Hagiwara, which is in error, rather it is Harrison et. al. that is the primary

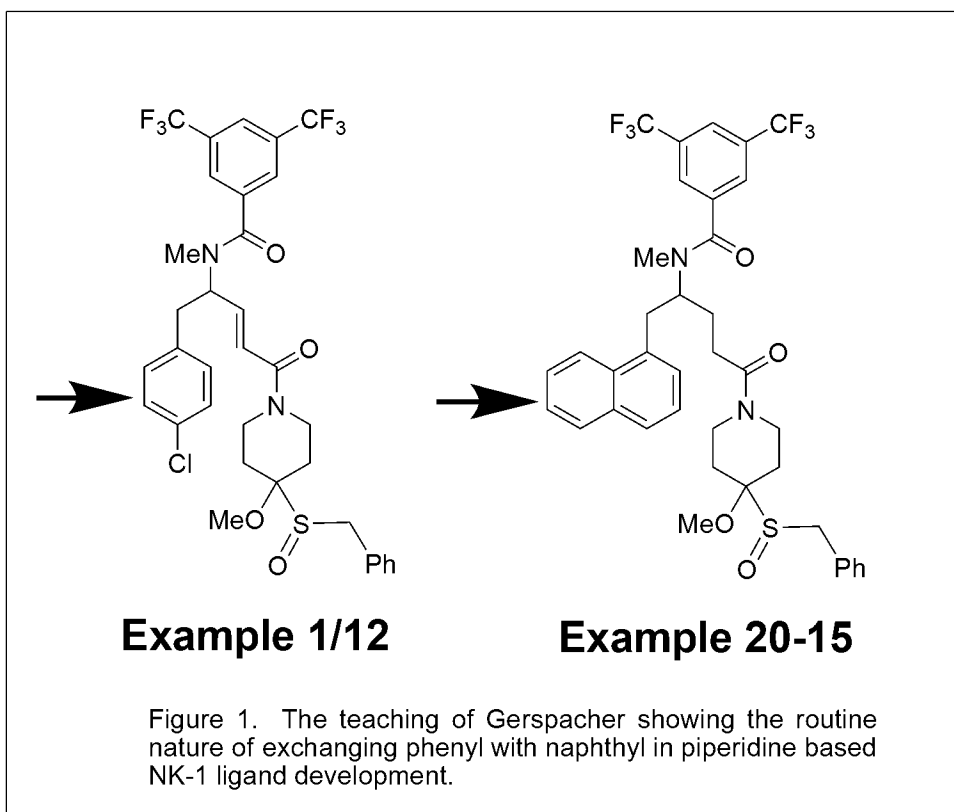
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reference now with Bernstein et. al. and Hagiwara. The applicants' representative has argued that the examiner is misguided in the characterization of the teaching of Hagiwara, as the remarks at pg. 5 indicate:

“Further, the office's characterization of the Hagiwara reference is misguided. The Hagiwara reference **DOES NOT** teach, as the Office alleges, that substitution of naphthyl for phenyl is "routine and desirable" in the field of NK1 receptor antagonists, as alleged in the Final Rejection at page 29.” Emphasis in original.

In the first aspect, as to whether or not it is routine to change phenyl to naphthyl in medicinal chemistry is without question and examples in the literature are ubiquitous. Clearly the Hagiwara reference shows the routine nature of such experimentation even when working on the exact same pharmacological target, the NK-1 receptor. However, as further evidence the examiner submits two other publications dealing with the development of **piperidine** based NK-1 receptor ligands, which show the routine nature of exchanging phenyl with naphthyl: Gerspacher et. al. WO199626183 and Vedani et. al. “Multiple-Conformation and Protonation-State Representation in 4D-QSAR: The Neurokinin-1 Receptor System” *Journal of Medicinal Chemistry*, **2000**, 43, 4416-4427.

Gerspacher teaches a series of compounds that differ only in the substitution of 4-chlorophenyl with naphthyl, compare the compounds on pgs. 108-114 (having 4-chlorophenyl) to the compounds on pgs. 119-121 (having naphthyl). In particular two piperidinyl NK-1 receptor ligands were prepared differing in phenyl vs. naphthyl, compounds 1/12 (pg. 119) and compound 20/15 (pg. 119), these are shown graphically below in Figure 1.



Vedani et. al. in a study on quantitative structure activity relationships at the NK-1 receptor with piperidine based ligands, included both compounds with naphthyl and phenyl moieties which were used interchangeably. See the Figure 2 compounds in Vedani et. al., in particular compound M15 and compound X32, as compared to the other compounds bearing phenyl rings (described as the B-ring therein).

With regard to the second aspect of “routine and desirable” applicants' representative has taken issue with as to whether or not it is “desirable” to exchange phenyl with naphthyl. Hagiwara et. al. teach Nk-1 antagonists bearing both phenyl and naphthyl moieties and did extensive SAR studies, and came to the following conclusion about the substitution of phenyl for naphthyl:

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“As shown in the previous paper,¹³ an aromatic functionality such as a L-phenylalanine is essential in this part. We therefore limited the modifications of this part to substituted L-phenylalanines or bicyclic aromatic L-amino acids. Electronic and lipophilic features of the substituent tend **not** to influence the binding activity, and some of bicyclic aromatic α amino acids including an L-2-naphthylalanine (**7k**) had potent binding activity. Regarding oral absorption, increasing lipophilicity such as introduction of a trifluoromethyl (**78**) or an L-2-naphthylalanine (**7k**) tends to enhance the activity. These facts imply that this class of compounds is absorbed through the lipid bilayer on the digestive tracts by a simple diffusion mechanism.”

Clearly increasing lipophilicity and in turn bioavailability or absorptivity, without affecting binding activity is desirable.

The applicants' representative has also argued that Hagiwara teaches away from the claimed invention by pointing to the fact that some of the naphthyl substituted Hagiwara compounds were less potent than the phenyl compounds. It is true that compound 7l and 7m of table 2 are less potent in the binding assay, however compound 7k was more potent. The compounds bearing substituted naphthyl moieties were only 3 to 4 times less potent, not 10 as suggested in the remarks. It is expected that some differences in activity will occur and the substitution of one naphthyl moiety for another to determine which is the best seems routine. Moreover it is clear that Harrison had all of these substituents on his phenyl ring and one naturally select such substituents for testing when making the naphthyl analogs. Given the nature of the Bernstein teaching it hardly seems relevant, since Bernstein determined exactly which naphthyl to choose. In addition a slight reduction in potency may be acceptable if an increase in bioavailability or absorptivity is obtained.

Now at least for compounds bearing naphthyl no further references are needed and these clearly make the naphthyl compounds obvious over the phenyl of Harrison et. al. without the need for Bernstein. It is the teaching of Bernstein that points exactly to these naphthyl

substitutions in the specific compounds in the specification (although no species are actually claimed). There can be no doubt that this was the preferred substituent.

The double patenting rejections have not been addressed and are maintained for the reasons of record.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-6, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et. al. WO 94/110165, cited on the IDS AND Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773 AND Hagiwara et. al. "Studies on Neurokinin Antagonists. 4. Synthesis and Structure-Activity Relationships of Novel Dipeptide Substance P Antagonists: N²-[(4R)-4-Hydroxy-1-([1-methyl-1H-indol-3-yl)carbonyl]-L-prolyl]-N-methyl-N-(phenylmethyl)-3-(2-naphthyl)-L-alaninamide and Its Related Compounds" *Journal of Medicinal Chemistry* **1994**, *37*, 2090-2099 in view of Gerspacher et. al. WO199626183 and Vedani et. al. "Multiple-Conformation and Protonation-State Representation in 4D-QSAR: The Neurokinin-1 Receptor System" *Journal of Medicinal Chemistry*, **2000**, *43*, 4416-4427.

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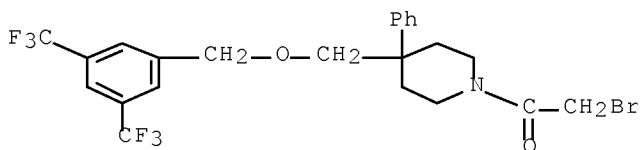
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

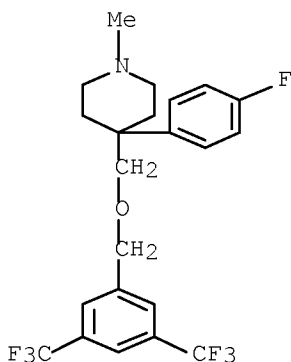
(MPEP 2141.01)

Harrison et. al. teaches NK-1 antagonists that are analogs of the compounds of the instant case that have the same utility. In particular the hundred or so compounds below:

RN 160376-77-2 CAPLUS
 CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(bromoacetyl)-4-phenyl- (9CI) (CA INDEX NAME)



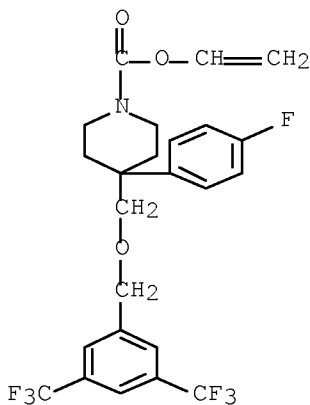
RN 160376-80-7 CAPLUS
 CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(4-fluorophenyl)-1-methyl- (9CI) (CA INDEX NAME)



Art Unit: 1625

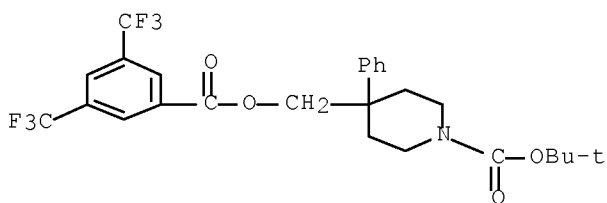
RN 160376-81-8 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(4-fluorophenyl)-, ethenyl ester (9CI) (CA INDEX NAME)



RN 160376-85-2 CAPLUS

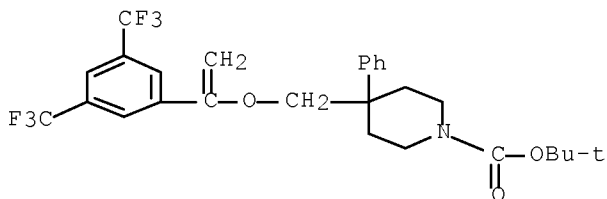
CN 1-Piperidinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)benzoyl]oxy]methyl]-4-phenyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 160376-86-3 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[[[1-[3,5-bis(trifluoromethyl)phenyl]ethenyl]oxy]methyl]-4-phenyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

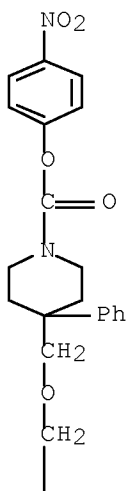
Art Unit: 1625



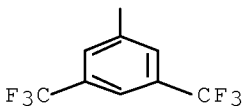
RN 160376-90-9 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-, 4-nitrophenyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



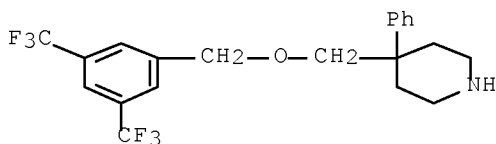
PAGE 2-A



RN 160375-92-8 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)

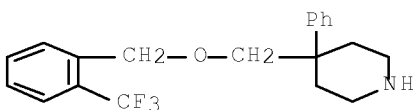
Art Unit: 1625



RN 160375-94-0 CAPLUS

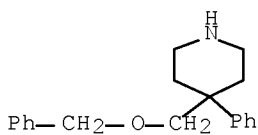
CN Piperidine, 4-phenyl-4-[[[2-(trifluoromethyl)phenyl]methoxy]methyl]-
(9CI)

(CA INDEX NAME)

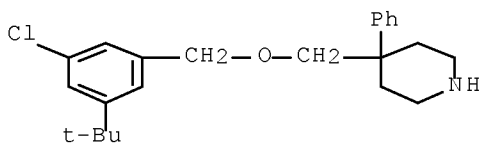


RN 160375-95-1 CAPLUS

CN Piperidine, 4-phenyl-4-[(phenylmethoxy)methyl]- (9CI) (CA INDEX NAME)



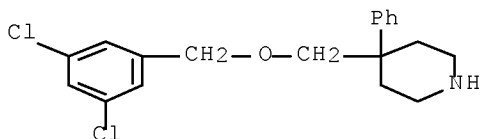
RN 160375-96-2 CAPLUS

CN Piperidine, 4-[[[3-chloro-5-(1,1-dimethylethyl)phenyl]methoxy]methyl]-4-
phenyl- (9CI) (CA INDEX NAME)

RN 160375-97-3 CAPLUS

CN Piperidine, 4-[[[3,5-dichlorophenyl]methoxy]methyl]-4-phenyl- (9CI) (CA
INDEX NAME)

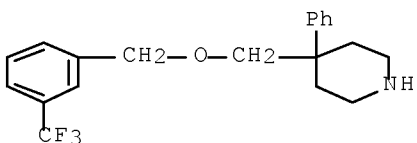
Art Unit: 1625



RN 160375-98-4 CAPLUS

CN Piperidine, 4-phenyl-4-[[[3-(trifluoromethyl)phenyl]methoxy]methyl]-
(9CI)

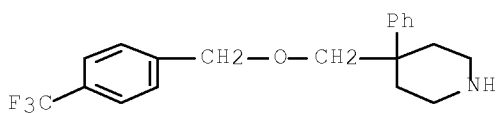
(CA INDEX NAME)



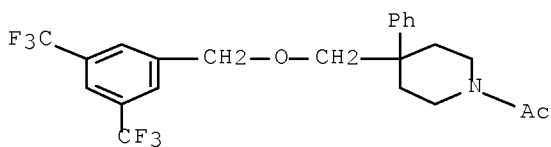
RN 160375-99-5 CAPLUS

CN Piperidine, 4-phenyl-4-[[[4-(trifluoromethyl)phenyl]methoxy]methyl]-
(9CI)

(CA INDEX NAME)



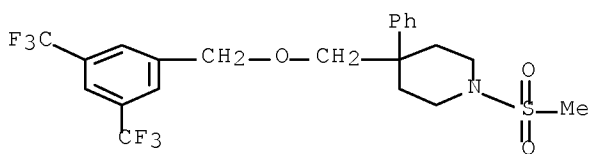
RN 160376-00-1 CAPLUS

CN Piperidine, 1-acetyl-4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-
(9CI) (CA INDEX NAME)

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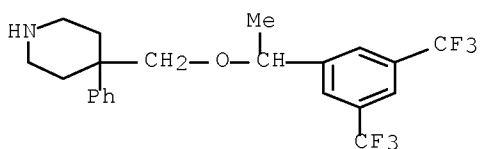
RN 160376-01-2 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(methylsulfonyl)-4-phenyl- (9CI) (CA INDEX NAME)



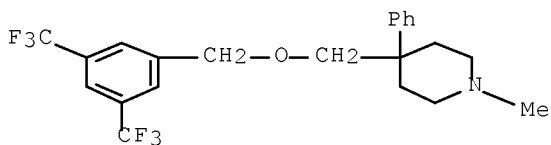
RN 160376-08-9 CAPLUS

CN Piperidine, 4-[[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)



RN 160376-09-0 CAPLUS

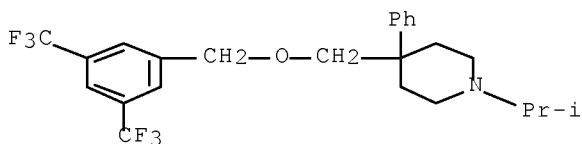
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-methyl-4-phenyl- (9CI) (CA INDEX NAME)



RN 160376-10-3 CAPLUS

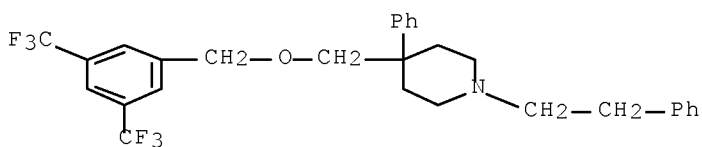
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(1-methylethyl)-4-phenyl- (9CI) (CA INDEX NAME)

Art Unit: 1625



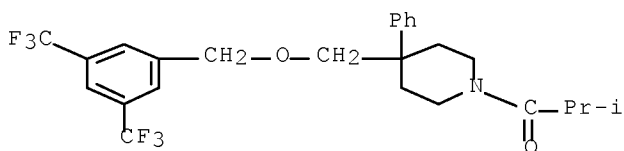
RN 160376-11-4 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-1-(2-phenylethyl)- (9CI) (CA INDEX NAME)



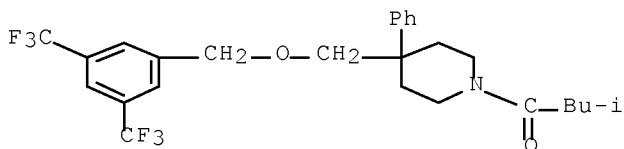
RN 160376-12-5 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(2-methyl-1-oxopropyl)-4-phenyl- (9CI) (CA INDEX NAME)



RN 160376-13-6 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(3-methyl-1-oxobutyl)-4-phenyl- (9CI) (CA INDEX NAME)

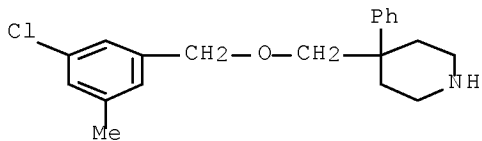


RN 160376-15-8 CAPLUS

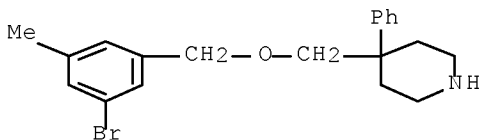
CN Piperidine, 4-[(3-chloro-5-methylphenyl)methoxy]methyl]-4-phenyl- (9CI)

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(CA INDEX NAME)

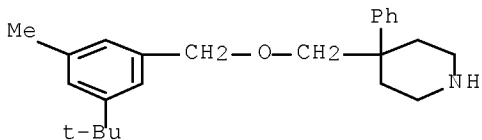


RN 160376-16-9 CAPLUS

CN Piperidine, 4-[[[3-bromo-5-methylphenyl]methoxy]methyl]-4-phenyl- (9CI)
(CA INDEX NAME)

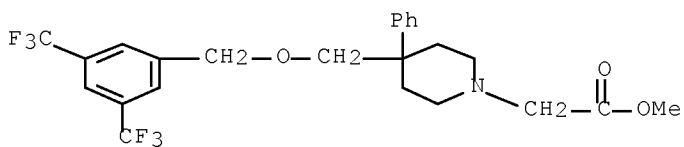
RN 160376-17-0 CAPLUS

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RN 160376-18-1 CAPLUS

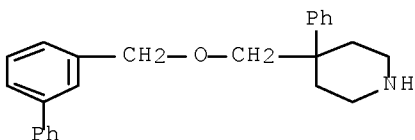
CN 1-Piperidineacetic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-, methyl ester (9CI) (CA INDEX NAME)



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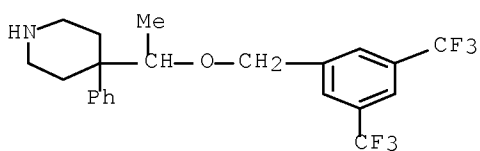
RN 160376-27-2 CAPLUS

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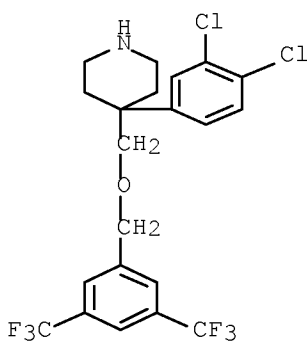
RN 160376-30-7 CAPLUS

CN Piperidine, 4-[1-[[3,5-bis(trifluoromethyl)phenyl]methoxy]ethyl]-4-phenyl- (9CI) (CA INDEX NAME)



RN 160376-31-8 CAPLUS

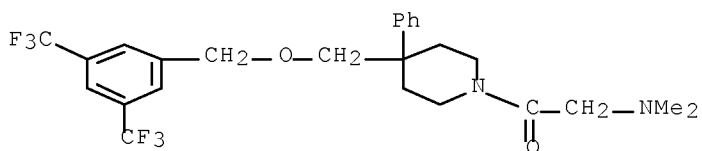
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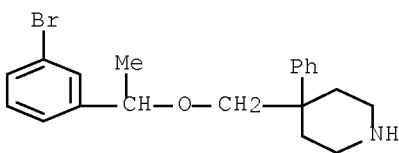
RN 160376-39-6 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy)methyl]-1-[(dimethylamino)acetyl]-4-phenyl- (9CI) (CA INDEX NAME)

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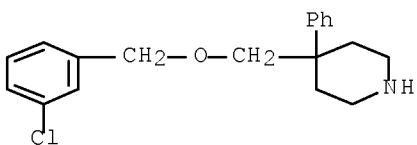


RN 160376-44-3 CAPLUS

CN Piperidine, 4-[[1-(3-bromophenyl)ethoxy]methyl]-4-phenyl-, hydrochloride
(9CI) (CA INDEX NAME)

● HCl

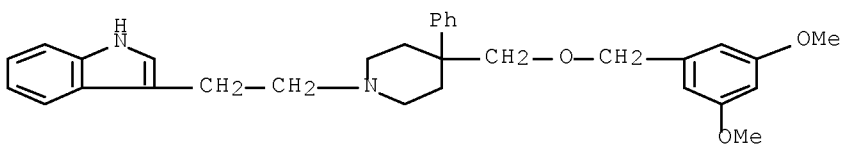
RN 160376-47-6 CAPLUS

CN Piperidine, 4-[[1-(3-chlorophenyl)methoxy]methyl]-4-phenyl-, hydrochloride
(9CI) (CA INDEX NAME)

● HCl

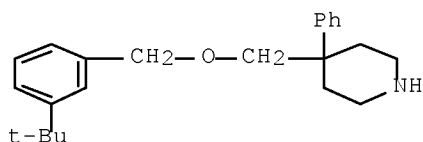
RN 160376-51-2 CAPLUS

CN 1H-Indole, 3-[2-[4-[[1-(3,5-dimethoxyphenyl)methoxy]methyl]-4-phenyl-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

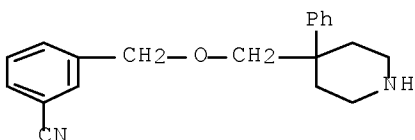


Art Unit: 1625

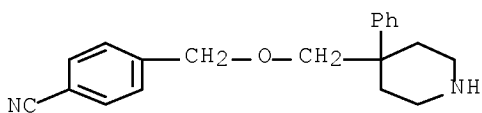
RN 160376-53-4 CAPLUS

CN Piperidine, 4-[[[3-(1,1-dimethylethyl)phenyl]methoxy]methyl]-4-phenyl-
(9CI) (CA INDEX NAME)

RN 160376-54-5 CAPLUS

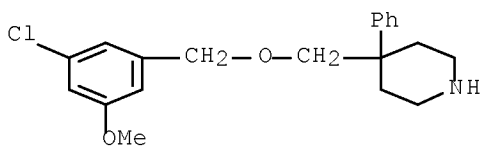
CN Benzonitrile, 3-[[[4-phenyl-4-piperidinyl)methoxy]methyl]- (9CI) (CA
INDEX NAME)

RN 160376-56-7 CAPLUS

CN Benzonitrile, 4-[[[4-phenyl-4-piperidinyl)methoxy]methyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

● HCl

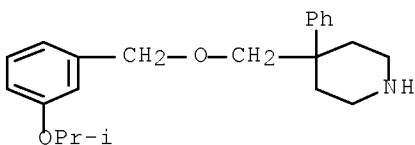
RN 160376-61-4 CAPLUS

CN Piperidine, 4-[[[3-chloro-5-methoxyphenyl)methoxy]methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

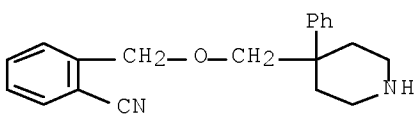
● HCl

Art Unit: 1625

RN 160376-66-9 CAPLUS

CN Piperidine, 4-[[[3-(1-methylethoxy)phenyl]methoxy]methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

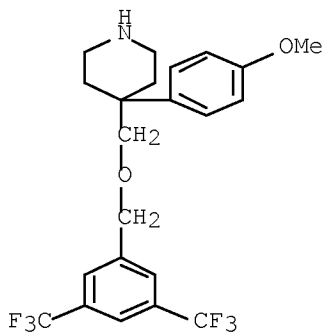
● HCl

CN Benzonitrile, 2-[[[4-phenyl-4-piperidinyl)methoxy]methyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

● HCl

RN 160376-69-2 CAPLUS

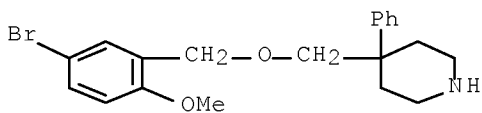
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(4-methoxyphenyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

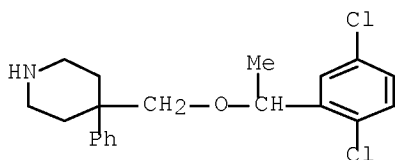
Art Unit: 1625

RN 160376-70-5 CAPLUS

CN Piperidine, 4-[[(5-bromo-2-methoxyphenyl)methoxy)methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

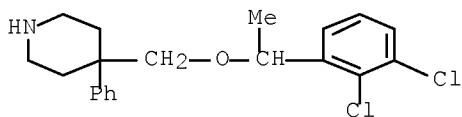
● HCl

RN 160376-71-6 CAPLUS

CN Piperidine, 4-[[1-(2,5-dichlorophenyl)ethoxy)methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

● HCl

RN 160376-72-7 CAPLUS

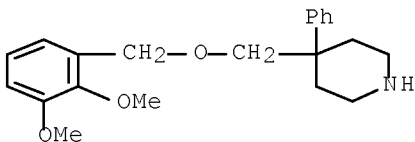
CN Piperidine, 4-[[1-(2,3-dichlorophenyl)ethoxy)methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

● HCl

RN 160376-73-8 CAPLUS

CN Piperidine, 4-[[(2,3-dimethoxyphenyl)methoxy)methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

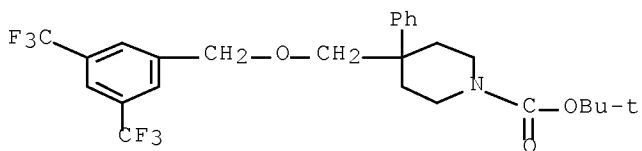
Art Unit: 1625



● HCl

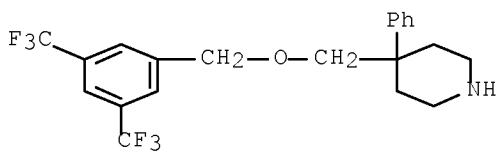
RN 160376-91-0 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 160376-92-1 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)

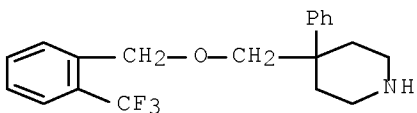


● HCl

RN 160376-94-3 CAPLUS

CN Piperidine, 4-phenyl-4-[[[2-(trifluoromethyl)phenyl]methoxy]methyl]-, hydrochloride (9CI) (CA INDEX NAME)

Art Unit: 1625

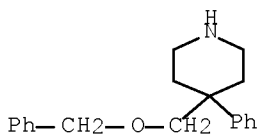


● HCl

RN 160376-95-4 CAPLUS

CN Piperidine, 4-phenyl-4-[(phenylmethoxy)methyl]-, hydrochloride (9CI)
(CA

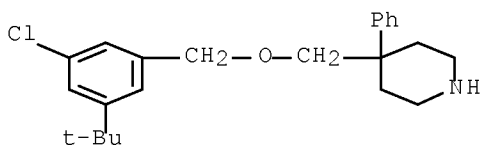
INDEX NAME)



● HCl

RN 160376-96-5 CAPLUS

CN Piperidine, 4-[[[3-chloro-5-(1,1-dimethylethyl)phenyl]methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)

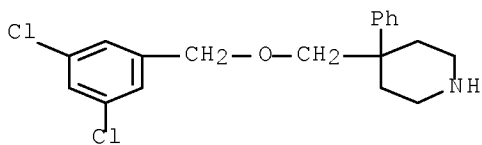


● HCl

RN 160376-97-6 CAPLUS

CN Piperidine, 4-[[[3,5-dichlorophenyl]methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)

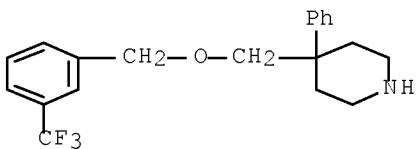
Art Unit: 1625



● HCl

RN 160376-98-7 CAPLUS

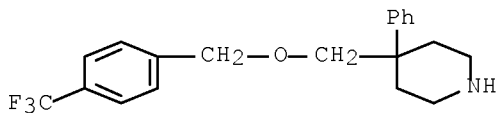
CN Piperidine, 4-phenyl-4-[[[3-(trifluoromethyl)phenyl]methoxy]methyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 160376-99-8 CAPLUS

CN Piperidine, 4-phenyl-4-[[[4-(trifluoromethyl)phenyl]methoxy]methyl]-, hydrochloride (9CI) (CA INDEX NAME)

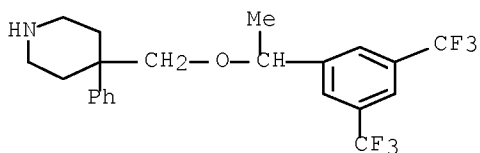


● HCl

RN 160377-03-7 CAPLUS

CN Piperidine, 4-[[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)

Art Unit: 1625



● HCl

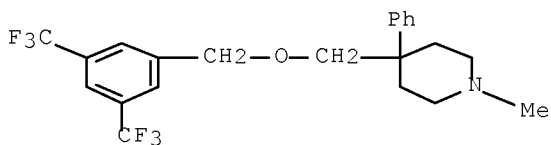
RN 160377-04-8 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-methyl-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 160376-09-0

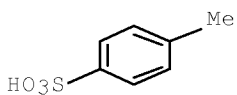
CMF C22 H23 F6 N O



CM 2

CRN 104-15-4

CMF C7 H8 O3 S



RN 160377-05-9 CAPLUS

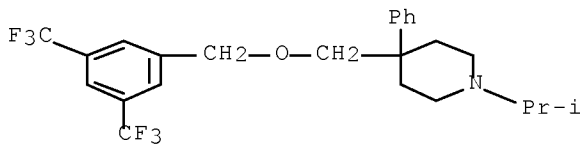
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(1-methylethyl)-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 160376-10-3

Art Unit: 1625

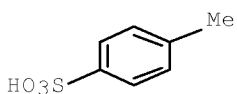
CMF C24 H27 F6 N O



CM 2

CRN 104-15-4

CMF C7 H8 O3 S



RN 160377-06-0 CAPLUS

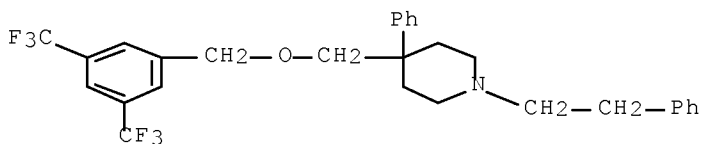
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-1-

(2-phenylethyl)-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 160376-11-4

CMF C29 H29 F6 N O

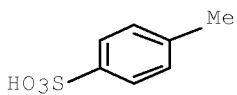


CM 2

CRN 104-15-4

CMF C7 H8 O3 S

Art Unit: 1625



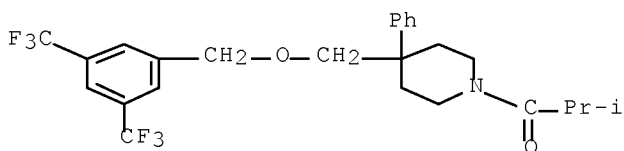
RN 160377-07-1 CAPLUS

CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(2-methyl-1-oxopropyl)-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 160376-12-5

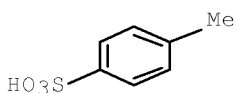
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CM 2

CRN 104-15-4

CMF C7 H8 O3 S



RN 160377-08-2 CAPLUS

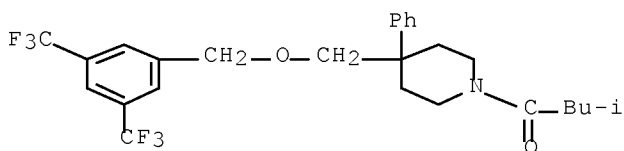
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(3-methyl-1-oxobutyl)-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 160376-13-6

CMF C26 H29 F6 N O2

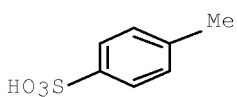
Art Unit: 1625



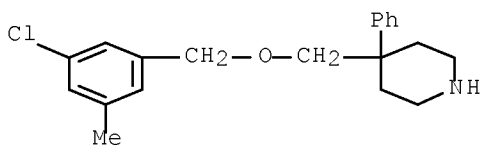
CM 2

CRN 104-15-4

CMF C7 H8 O3 S



RN 160377-09-3 CAPLUS

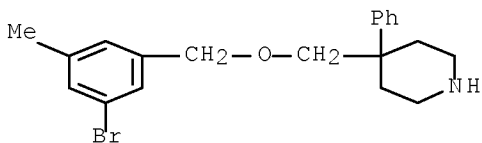
CN Piperidine, 4-[[(3-chloro-5-methylphenyl)methoxy]methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

● HCl

RN 160377-10-6 CAPLUS

CN Piperidine, 4-[[(3-bromo-5-methylphenyl)methoxy]methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

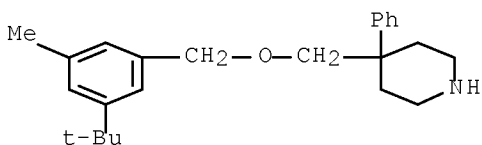
Art Unit: 1625



● HCl

RN 160377-11-7 CAPLUS

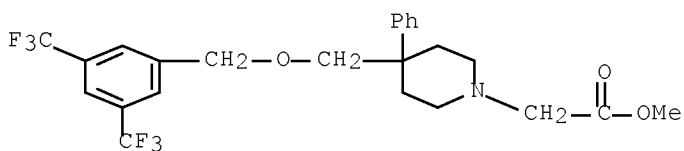
CN Piperidine, 4-[[[3-(1,1-dimethylethyl)-5-methylphenyl]methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 160377-12-8 CAPLUS

CN 1-Piperidineacetic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-, methyl ester, hydrochloride (9CI) (CA INDEX NAME)

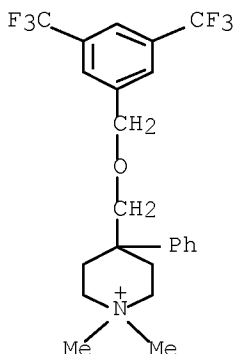


● HCl

RN 160377-13-9 CAPLUS

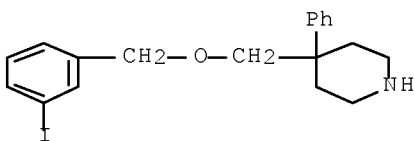
CN Piperidinium, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1,1-dimethyl-4-phenyl-, iodide (9CI) (CA INDEX NAME)

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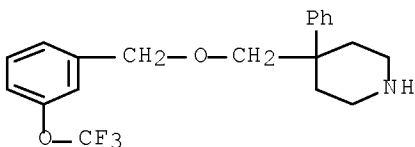
RN 160377-34-4 CAPLUS

CN Piperidine, 4-[[[3-iodophenyl)methoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)



RN 160377-37-7 CAPLUS

CN Piperidine, 4-phenyl-4-[[[3-(trifluoromethoxy)phenyl]methoxy]methyl]-, hydrochloride (9CI) (CA INDEX NAME)



Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773, in a related series of piperidine compounds, started with the known selective antagonist SR48968, and modified the phenyl portion by screening a diverse set of compounds where the phenyl was replaced with

"over 100 aryl, heteroaryl and arylalkyl groups". In the words of Bernstein the result of this study was "the most potent, dual acting compound to come out of this array was the naphthamide **2a**". Bernstein goes on to describe that "to follow-up the discovery of this naphthamide we explored the effect of substituents on the naphthalene ring." It is interesting that 3-cyano-naphthyl was the preferred substituent, as in compound **4**. This 3-cyano naphthyl group is also the preferred substituent of the instant case and is what distinguishes these compounds from those of Harrison et. al. There can be no doubt that this was the preferred substituent.

Hagiwara et. al. teach Nk-1 antagonists bearing both phenyl and naphthyl moieties and did extensive SAR studies, and came to the following conclusion about the substitution of phenyl for naphthyl:

"As shown in the previous paper,¹³ an aromatic functionality such as a L-phenylalanine is essential in this part. We therefore limited the modifications of this part to substituted L-phenylalanines or bicyclic aromatic L-amino acids. Electronic and lipophilic features of the substituent tend **not** to influence the binding activity, and some of bicyclic aromatic α amino acids including an L-2-naphthylalanine (**7k**) had potent binding activity. Regarding oral absorption, increasing lipophilicity such as introduction of a trifluoromethyl (**78**) or an L-2-naphthylalanine (**7k**) tends to enhance the activity. These facts imply that this class of compounds is absorbed through the lipid bilayer on the digestive tracts by a simple diffusion mechanism."

While not remarkably similar in structure, the compounds of Hagiwara teach that in the field of NK-1 receptor antagonists a substitution of naphthyl for phenyl is routine and desirable.

Ascertainment of the difference between the prior art and the claims

The instant claims differ from the compounds of Harrison et. al only in the substitution of a naphthyl group for the phenyl. Harrison's phenyl ring has a variety of substituents including halogens, alkoxy, CN, and alkyl groups. Both Bernstein and Hagiwara teach the interchange of naphthyl for phenyl. Hagiwara shows that the change made to the compounds of Harrison et. al.

to be routine, equivalent to the phenyl of Harrison and desirable in this very narrow field of NK-1 receptor antagonists. Bernstein teaches the precise naphthyl groups exemplified in the specification bearing (CN) groups.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Harrison et. al. to produce the instant invention. Analogs differing only in the substitution of phenyl for naphthyl, are *prima facie* obvious, and require no secondary teaching when the utility is the same. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to replace phenyl with naphthyl. Harrison suggests that lipophilicity of the aryl moiety to be important since numerous compounds bearing the lipophilic CF₃ group were prepared, thus naphthyl being slightly more lipophilic would have increased potency. one of ordinary skill would recognize the lipophilicity of naphthyl as being similar to the various phenyl groups of Harrison, and recognize their interchangeability. Nearly all of his compounds bear greasy groups, including CF₃, phenyl, t-butyl, bromine etc. Bernstein teaches the exact modification (down to the very precise substituents on the naphthyl ring), thus the use of naphthyl in these NK1-antagonists and the substitution of naphthyl for phenyl was very well known even in this very small field. Moreover Hagiwara, shows the equivalence of phenyl and naphthyl, and desirability of this change which increases the lipophilicity of NK-1 antagonists which in turn increases bioavailability without altering binding, which would be a strong motivation to make the invention of the instant claims. There can be no doubt that changing phenyl in the compounds of Harrison to naphthyl is an obvious change.

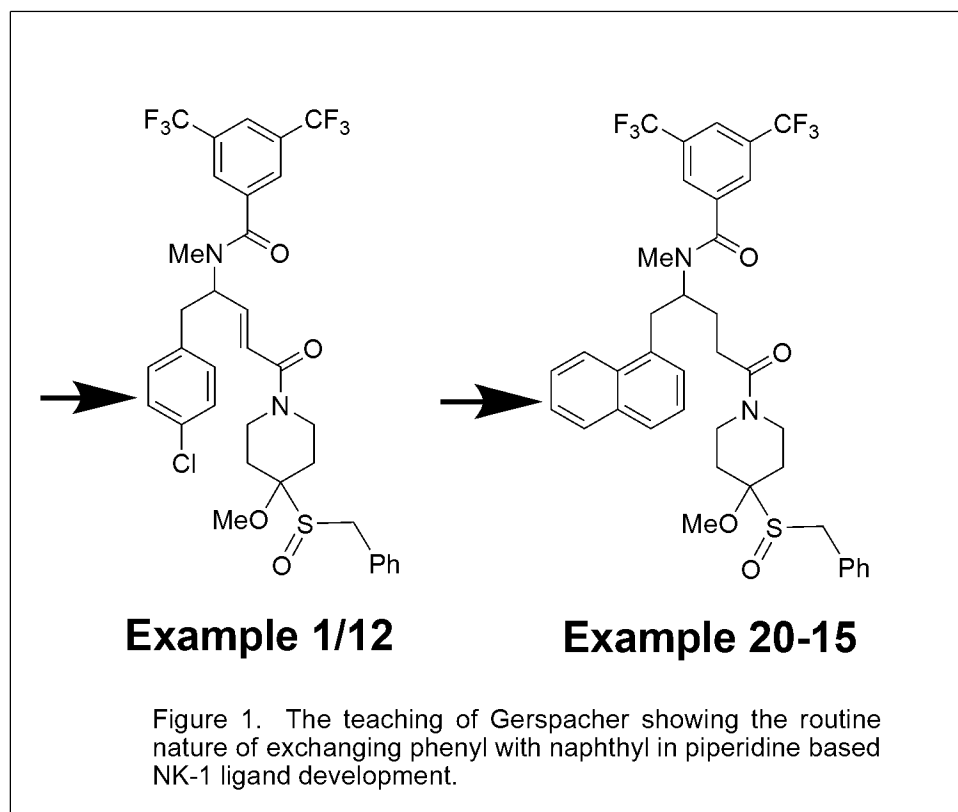
Ex parte WESTFAHL, 136 USPQ 265 (Bd. Pat. App. & Int. 1962):

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“Appellant relies upon the case of *In re Jones*, 32 CCPA 1020, 1945 C.D. 304, 579 O.G. 148, 149 F.2d 501, 65 USPQ 480, as supporting the patentability of claim 8 because in that case a naphthyl compound was held to be patentable over the corresponding phenyl compound. However, the rejection in that case was based upon the premise, held to be untenable by the court, that benzene and naphthalene are members of a homologous series. In the present case, **the examiner does not rely upon any theory of homology but has cited a reference (Richter II) teaching that naphthalene is very similar to benzene and forms a series of analogous derivatives.**”

As further evidence the examiner submits two other publications dealing with the development of **piperidine** based NK-1 receptor ligands, which show the routine nature of exchanging phenyl with naphthyl: Gerspacher et. al. WO199626183 and Vedani et. al. “Multiple-Conformation and Protonation-State Representation in 4D-QSAR: The Neurokinin-1 Receptor System” *Journal of Medicinal Chemistry*, **2000**, 43, 4416-4427.

Gerspacher teaches a series of compounds that differ only in the substitution of 4-chlorophenyl with naphthyl, compare the compounds on pgs. 108-114 (having 4-chlorophenyl) to the compounds on pgs. 119-121 (having naphthyl). In particular two piperidinyl NK-1 receptor ligands were prepared differing in phenyl vs. naphthyl, compounds 1/12 (pg. 119) and compound 20/15 (pg. 119), these are shown graphically below in Figure 1.



Vedani et. al. in a study on quantitative structure activity relationships at the NK-1 receptor with piperidine based ligands, included both compounds with naphthyl and phenyl moieties which were used interchangeably. See the Figure 2 compounds in Vedani et. al., in particular compound M15 and compound X32.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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One of ordinary skill is also one of “ordinary creativity, not an automaton”. See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT “An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-6, 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/539,140 in view of Elliot et. al. *Bioorganic & Medicinal Chemistry Letters* 12 (2002) 1755–1758.

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This is a provisional obviousness-type double patenting rejection. The instant claims differ from those of the '140 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists.

"Table 1 summarises the effect of modifications to the amide linker of 2. Throughout, trans-isomers have higher affinity than the corresponding cis-isomers. **A number of different linkers are tolerated, most notably the amides 2 and 15, the amine 17 and ether 23.** The relatively poor affinity of the propyl linker 24 (hNK₁ IC₅₀ 40nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor." Pg. 1756-1757 Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758

Table 1. Linker replacements

Compd	-L-	Stereochemistry	hNK ₁ IC ₅₀ (nM) ^a
11		<i>cis</i> -	150 ± 80
2		<i>trans</i> -	0.34 ± 0.10
12		<i>cis</i> -	250 ± 26
13		<i>trans</i> -	6.3 ± 2.5
14		<i>cis</i> -	85 ± 46
15		<i>trans</i> -	0.70 ± 0.44
16		<i>cis</i> -	82 ± 0
17		<i>trans</i> -	1.7 ± 0.6
18		<i>cis</i> -	140 ± 49
19		<i>trans</i> -	2.5 ± 0.6
20		<i>cis</i> -	50% @ 1000
21		<i>trans</i> -	120 ± 99
22		<i>cis</i> -	59 ± 18
23		<i>trans</i> -	4.2 ± 1.9
24		1:1 <i>cis</i> - and <i>trans</i> -	40 ± 3

^aDisplacement of [¹²⁵I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean ± SD (n = 3).⁵

7. Claims 1-6, 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No.

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10/525,303. The claims are coextensive in scope. in view of Elliot et. al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758.

This is a provisional obviousness-type double patenting rejection. The instant claims differ from those of the '303 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists.

“Table 1 summarises the effect of modifications to the amide linker of 2. Throughout, trans-isomers have higher affinity than the corresponding cis-isomers. **A number of different linkers are tolerated, most notably the amides 2 and 15, the amine 17 and ether 23.** The relatively poor affinity of the propyl linker 24 (hNK₁ IC₅₀ 40nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor.” Pg. 1756-1757 Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758

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^aDisplacement of [¹²⁵I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean ± SD (n = 3).^a

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Janet L. Andres/
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